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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/635,949	08/10/2000	Richard A. Shimkets	15966-559 (CURA-59)	5151

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/635,949	SHIMKETS ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 9, 2004 has been entered.

Claim Disposition

2. Claims 1-41 have been canceled. Claims 42-51 are pending and are under examination.

3. The following grounds of rejection are or remain applicable :

Claim Rejections-Utility Rejections Under 35 U.S.C. § 101 And 35 U.S.C. 112, First Paragraph

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 42-51 remain rejected under 35 U.S.C. 101 because the claimed invention lacks substantial utility.

The claims are directed to nucleic acids encoding proteins that are described as useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. However, the disclosure does not identify the protein families that are similar to the claimed protein. In addition, there is no indicia as to the function assigned to the protein that is suppose to be similar to other protein families. The prior art teaches that "numerous cases exists in which proteins of very different current functions are homologous in that they evolved from a common ancestor and will match with significant sequence similarity. The prior art also teaches that the practice of assigning functions by sequence similarity is dangerous because many of the automatic predictions by most of the software robots are erroneous", Smith et al., Nature Biotechnology, vol. 15, pages 1222-1223, November 1997 is one of many such references. The claimed polynucleotides are not supported by a substantial asserted utility. Identifying a polynucleotide as encoding a PROX polypeptide does not endow the polynucleotide with such a utility. Identifying a protein as having a limited homology to another family of proteins, which is not known to be a member of a family of similarly acting factors with identifiable functional regions, does not indicate what function it and thus the encoding polynucleotide might have. The specification states that the claimed PROX nucleic acid and the encoding protein can be used to treat or prevent or delay a PROX-associated disorder in a subject, however, there is no specific disease or specific function that is suggested by this limited homology. The specification indicates that the claimed protein is over expressed in certain tissues thus, the clone has use as a probe. Tissue-specific expression does not

rely on specific properties or functions of the encoded protein. Further, the specification does not disclose any diseases or conditions known to be associated with the encoded protein. Note also that the over expression demonstrated in the instant specification is of the nucleic acid which does not unequivocally mean that there will be over expression of the protein. Furthermore, the specification lists several pages of expression levels in several different tissues, which indicates that the probe is not tissue specific. The asserted utility disclosed in the instant specification exemplifies a real world context of use, where further research would be required to identify a disease in which the encoded protein is involved and to identify the families that are homologous and their functions. Thus, the polynucleotide lacks specific and substantial utility.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 42-51 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either substantial asserted utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

6. Claims 42-51 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification on page 2 states that the invention is based on nucleic acids and secreted polypeptides encoded thereby and fragments, homologs, analogs and derivatives thereof, referred to as PROX and the specification does not provide a definition for "PROX". The specification also states that the methods are provided to treat or prevent or delay a PROX-associated disorder or proliferation-associated disorder in a subject (see page 4). However, no specific disease or disorder is described or exemplified. On page 6 of the disclosure it is stated that PROX nucleic acids and polypeptides are useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. However, the specification does not demonstrate or describe any such proteins in association with the claimed invention. The disclosure states that PROX nucleic acids and polypeptides can be used to identify cell types based on the presence or absence of various PROX nucleic acids according to the invention, however, the tables in the disclosure show a broad spectrum of tissue types, thus, specificity is lacking.

On pages 56-57 of the instant specification it is disclosed that Clone 16467945.88 (PROX 17), nucleic acid SEQ ID NO: 33 that encodes polypeptide SEQ ID NO: 34 are highly over expressed in certain breast cancer cell lines, ovarian cancer cell lines, renal cancer cell lines and colon cancer cell lines. Further, the encoded protein is strongly suppressed in lung cancer cell lines in comparison with normal lung cells. Thus, the disclosure asserts that this clone may be used as a selective probe for detection or diagnosis of these cancers and that the clones or their genes products may be useful

therapeutics or target in treatment of such cancers (see also pages 93 and 104 for other asserted use for the protein). The results are said to be presented in Example 16. Example 16 found on pages 150-151 of the instant specification exemplifies Clone 11692010.051 which according to Table 1 found on pages 5-6 represents nucleic acid SEQ ID NO: 5 that encodes polypeptide SEQ ID NO: 6. The disclosure states that the example demonstrates that 11692010 gene product inhibits trypsin at a 50% inhibitory level. It is further stated that proteins exhibiting some similarity to the clone 11692010.051 protein can be potentially used for: 1) the stimulation of growth and motility of keratinocytes; 2) modulation of angiogenesis and tumor vascularisation; 3) the inhibition of the growth of cancer cells (i.e. melanomas); 4) modulation of skin inflammation and 5) modulation of epithelial cell growth. In addition, the protein encoded by Clone 11692020.051 has some degree of similarity to fibromodulin, a protein that potentially regulates extracellular matrix remodeling. Note that the nucleic acid and the encoded protein exemplified in Example 16 is not Clone 16467945.88 (PROX 17), nucleic acid SEQ ID NO: 33 that encodes polypeptide SEQ ID NO: 34. Clone 11692010.051, nucleic acid SEQ ID NO: 5 (2852 nucleotides) that encodes polypeptide SEQ ID NO: 6 (652 residues) is structurally and physically distinct from Clone 16467945.88 (PROX 17), nucleic acid SEQ ID NO: 33 (2112 nucleotides) that encodes polypeptide SEQ ID NO: 34 (584 residues). Thus the statement that proteins exhibiting some similarity to the clone 11692010.051 protein can be potentially used for 1) the stimulation of growth and motility of keratinocytes; 2) modulation of angiogenesis and tumor vascularisation; 3) the inhibition of the growth of cancer cells (i.e. melanomas); 4) modulation of skin inflammation and 5) modulation of epithelial cell growth is not demonstrated in Example 16 as there is no indication of what percent homology to equate with “some similarity” and no examples are provided of Clone 16467945.88

inhibiting trypsin. Based on the variations between the two sequences there is no indication that the same function ascribed to the clone exemplified in Example 16 is retained. Further, the specification indicates that Clone 11692020.051 has some degree of similarity to the protein fibromodulin and there is no indication of what percent homology to equate with "some degree of similarity". A search of the claimed sequence for Clone 16467945.88 did not produce any results that indicated the sequence is homologous to a protein of the fibromodulin family. Thus, the activity indicated for this protein cannot be assigned to the protein encoded by Clone 16467945.88. Therefore, the instant specification provides no evidence of the asserted function for the encoded protein.

The claims are directed to a nucleic acid and the encoding protein and there is no indicia as to the biological activity of the protein per se. Additionally, there is no analogous art.

The specification on page 93 indicate that the nucleic acid molecules, proteins, protein homologous and antibodies can be used in the following methods: screening assays, detection assays, predictive medicine, and methods of treatment. However, no standardized screening assay is demonstrated. Additionally, the specification provides no demonstration of specific detection assays or any methods of treatment in association with a specific disease or disorder. It is noted that pages 132+ indicate that Tables 22 and 23 provide primer sequence information and the relative expression results for clones that are highly expressed in central nervous system tumors and melanomas and suppression in colon cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer etc. However, it does not provide evidence of expression of the claimed polypeptide as the expression of the polynucleotides does not unequivocally mean expression of the polypeptides. Typically, when a polynucleotide is expressed in

a tissue-specific manner, the polypeptides encoded thereby are also similarly expressed in a tissue-specific manner, one can assume that the polypeptides are expressed in a tissue-specific manner, in the ovary, breast etc. However, absent evidence of this, it is also reasonable to assume that expression of the DNA may not result in expression of the protein. Note also that pages 133-150 lists all kinds of tissues and expression levels, thus it appears that expression is not tissue specific.

Thus, absent guidance via data as to the use of the encoded protein and a showing of a probe that is specific one of skill in the art would have to engage in undue experimentation to practice the claimed invention. Therefore, the instant specification lacks adequate written description.

7. Applicant's response filed June 9, 2004 has been considered, however was not found persuasive, thus, the rejections of record remains. With regard to the rejection under 35 U.S.C. 101 applicant contends that the claimed invention has at least one substantial and specific utility and points to the use of the DNA in diagnostic applications involving cancer, specifically breast, ovarian, renal and colon cancers and the over expression in the above tissues of the DNA. Applicant also contends that the DNA has use as a selective probe for detection or diagnosis of these specific cancers. Example 15 is pointed to as demonstrating "highly over-expression" of clones in certain breast cancer cell lines, ovarian cancer cell lines, renal cancer cell lines and colon cancer cell lines. Applicant's assertion of the utility regarding the above diseases is not substantial as the specification does not disclose any evidence to support the assertion. There is no evidence or example that the PROX-17 is not expressed in healthy tissues.

It could be a constitutively expressed gene, and thus would not be useful in developing drugs for any disease. Even if it is differentially expressed in cancerous tissues, for example, there is no indication regarding how to develop a drug to treat cancer based on PROX-17 and expression of the DNA does not equate necessarily to expression of the protein.

Applicant makes the point that PROX 17 is "highly over-expressed"; over-expression simply means more and highly over-expressed would mean even more, however, what is the utility for the "over-expression or highly over-expression" of the clone in cell lines, what does it do, especially since expression whether "over-expression or highly over-expression" is seen in several different cell lines, indicating the lack of specificity. The specification does disclose any particular condition wherein there is a deficiency, overproduction, or altered form of the claimed polypeptide. The fact that the polynucleotide can be found in libraries of for example, cells isolated from cancerous tissues, immortalized cell lines, immune system cells and cells from tissues affected by inflammatory conditions would not indicate to one of ordinary skill in the art that PROX is involved with any of these conditions. For diagnosing a disease associated with PROX, the disclosure would need to identify symptoms associated with such a disease and none is provided. With regard to probes, this asserted utility is not specific as such can be done with any polynucleotide.

Applicant state that the present rejection is directed to irrelevant subject matter as the restriction requirement separated polynucleotide from polypeptide, however, this statement is inaccurate. The claims are directed to "an isolated polynucleotide

comprising a nucleic acid sequence encoding a polypeptide of SEQ ID NO:". As the encoded protein is recited in the claim, the issues raised are relevant. The DNA is defined as encoding a protein, thus, the function/activity of the protein is relevant. As no clear function is ascribed, it appears that the claimed DNA encodes a protein that has no function *per se*. Thus, significant further experimentation would be required of the skilled artisan to identify individuals who would benefit from such a drug and then to determine best course of treatment. Thus, the asserted utility has not been presented in mature form and the rejection remain.

Applicant's comments regarding the rejection under 35 U.S.C. 112, first paragraph (enablement) is noted. However, due to the large quantity of experimentation necessary to determine an activity or property of the disclosed PROX-17 such that it can be determined how to use the claimed polynucleotides encoding PROX-17, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the fact that the claims fail to recite a particular biological activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention, therefore, the rejection under 35 U.S.C. 112, first paragraph enablement remains. This response is deemed sufficient to address arguments presented on pages 4-9.

With regard to the rejection under 35 U.S.C. 112, first paragraph written description applicant contends that "applicant is allowed to be their own lexicographer

and has chosen "PROX". The issue raised is not the naming of the molecule, but what does the molecule do. The nucleic acid is given the function of encoding a PROX protein, however, there is no further indication of function or demonstration of activity.

It is also stated (page 10 of the response) that the instant specification provides at least 17 novel clones, PROX-1-17 at the time of filing, indicating possession. However, according to the MPEP, section 2163, "an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997)*. Therefore, a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence (see MPEP 2163).

Applicant states that the claims pertain to "polynucleotide SEQ ID NO:33 encoding the polypeptide SEQ ID NO:34", therefore, is adequately described. Note that the language presented above does not accurately represent the claims as filed and the instant specification needs to provide an adequate written description of the structure/function relationship of the claimed products. The issue is that the function of the DNA is to encode a protein and the specification does not adequately describe what the protein does, thus, it appears that the claimed DNA encodes a protein that is not active.

Applicant points to examples in the specification (i.e., Example 15), "as providing differential tissue expression indicating an association with a cancerous tissues, however, as stated above, over expression in cell lines does not provide the answer to the question "what does it do". No correlation is provided between a specific disease and the over expression found in several cell lines. The over-expression evidenced in breast, ovarian, renal and colon cancer tissue is not specific and note that the specification provides expression in other tissues as well. The argument presented that SEQ ID NO:33 can be used to design probes is also not a specific. On page 13 it is stated that "what is required for patentability is that the claimed invention be novel, nonobvious and useful". The specification does not adequately describe the encoded protein or function, hence does not meet the burden of novel, nonobvious and useful. Therefore it appears that the claimed DNA encodes a non-functional protein.

The specification indicates that Clone 11692020.051 has some degree of similarity to the protein fibromodulin. Note that the prior art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech., vol. 18, pages 34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, page 36). Therefore, based on the discussions above concerning the specific example of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to

use the claimed polynucleotide to make biologically active PROX-17 without resorting to undue experimentation to determine what the specific biological activities of the PROX-17 are. Thus, the rejection of record remains. This response is deemed sufficient to address the issues raised on pages 9-16.

Conclusion

8. No claims are allowable.

9. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-

0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner

Jon P. Weber, Ph.D.
Primary Examiner